

## REMARKS

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

### I. Status of the Claims

Claims 57-98 are pending, and claims 93-98 are withdrawn. Thus, claims 57-98 are pending and subject to examination on the merits.

### II. Claim Rejections – 35 U.S.C. § 102

Claims 57-93 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Zhu *et al.*, ORGANIC LETTERS 5(8):1257-60 (2003). According to the Examiner, Zhu discloses “using the instant compounds (see compound 4’ on p. 1259) to detect an organophosphatase in a sample.” Office Action at 2. Applicants respectfully traverse this ground of rejection.

Zhu fails to anticipate the claimed invention, because Zhu does not disclose the claimed compounds. For example, “R<sup>6</sup> and R<sup>8</sup> [of the compound of formula I] are halo.” Compound 4’ of Zhu does not contain any halos at the R<sup>6</sup> and R<sup>8</sup> positions. Compound 4’ of Zhu also contains a –COOH group, which is used as part of the attachment chemistry, but R<sup>4</sup> of the claimed compounds does not include a –COOH group. Because Zhu does not disclose the claimed compounds, it cannot anticipate the claimed invention.

Claims 65-93, which are method claims, are further distinguished from Zhu for at least two reasons.

*First*, Zhu does not teach or suggest that compound 4’ is a substrate for phosphatase. Zhu discloses compound 4’ as “the protected form of 4.” Zhu at p. 1259, left col. Specifically, “[t]he phosphate group in 4’ was temporarily blocked to ensure site-specific immobilization upon spotting onto the glass slide . . . .” Zhu at p. 1259, left col. Because Zhu discloses compound 4’ as being a protected form of the actual substrate, Zhu teaches against the use of compound 4’ as a substrate for phosphatase.

*Second*, Zhu is directed to detecting the presence of phosphatases rather than organophosphatases, as claimed. Phosphatases and organophosphatases are distinct classes of enzymes, and substrates for one class of enzyme are not necessarily substrates for another class of enzyme. Specifically, organophosphate is the general name for esters of phosphoric acid. Phosphates are the most pervasive organophosphorus compounds. A phosphatase is an enzyme that removes a phosphate group from its substrate by hydrolysing phosphoric acid monoesters into a phosphate ion and a molecule with a free hydroxyl group. Organophosphates refers to a group of organophosphorus compounds acting on the enzyme acetylcholinesterase. The term is used often to describe virtually any organic phosphorus-containing compound, especially when dealing with neurotoxins. Many of organophosphates contain C-P bonds. Others are di- or tri- ester of phosphoric acid. Phosphatases catalyze hydrolysis of the monoester of phosphoric acid, but organophosphatases catalyze hydrolysis of di-, tri-esters of phosphoric acid, as well as other compounds containing C-P or F-P bonds, like soman, sarin, VX, and diisopropyl phosphorofluoridate. Thus, one of skill in the art would have no reason to believe that any of the compounds disclosed by Zhu could be used to detect organophosphatases, as claimed. In fact, Applicants tested a wide array of compounds and found that compound 4 is unacceptable as a substrate for measuring organophosphatase activity.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

### **III. Claim Rejections – 35 U.S.C. § 103**

#### **A. *Zhu et al.*, ORGANIC LETTERS 5(8):1257-60 (2003)**

Claims 57-93 stand rejected under 35 U.S.C. § 103 as allegedly obvious over *Zhu et al.*, ORGANIC LETTERS 5(8):1257-60 (2003). According to the Examiner, “the slight differences in particular (coumarin-7-yl)phosphate and/or particular location of the enzyme relative to said (coumarin-7-yl)phosphate would have been obvious to one of ordinary skill in the art.” Office Action at 2. Applicants respectfully traverse this ground of rejection.

Zhu fails to render obvious the claimed invention for the same reasons discussed above in Section II. Specifically, Zhu fails to teach the claimed compounds, and there is no evidence or explanation of record as to why one of skill in the art would modify Zhu's compounds to arrive at the claimed compounds.

Moreover, Zhu's compound 4 is directed to use with phosphatases rather than organophosphatases. As noted above, these are two distinct classes of enzymes and substrates for phosphatases are not necessarily substrates for organophosphatases. Thus, one of skill in the art would have no reason to believe that Zhu's compound 4 could be used to detect organophosphatases. In fact, testing would reveal that compound 4 is not a suitable substrate for measuring organophosphatase activity.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**B. Gee *et al.*, Analytical Biochemistry 273:41-48 (1999)**

Claims 57-93 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Gee *et al.*, ANALYTICAL BIOCHEMISTRY 273:41-48 (1999)<sup>1</sup>. According to the Examiner, "[Gee] discloses the use of phosphates based on 6,8-difluorumbelliferone to detect organophosphatase." Office Action at 3. Applicants respectfully traverse this ground of rejection.

The claimed invention is based, in part, on the discovery that diethyl phosphate is the minimal group required for specific recognition by organophosphatases. Connection of this specific group to common fluorophore, like difluoro -methylumbelliferyl, will result in a substrate specifically hydrolyzed by organophosphatases, but not phosphatases or any other hydrolytic enzyme. The data in the specification demonstrates the specificity of the claimed substrate.

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<sup>1</sup> The Examiner notes that Gee "anticipate[s]" the claims. However, Applicants understand this to be an obviousness rejection, because the rejection is included in the Section 103 portion of the Office Action with the other obviousness rejections.

Gee generally discloses a more stable and fluorescent version of methylumbelliferyl, difluoro-methylumbelliferyl. Methylumbelliferyl as well difluoro-methylumbelliferyl are used as base fluorophore for detection of phosphatase or glucosidase activity.

Gee fails to teach or suggest the claimed invention, because Gee makes no mention of using DiFMUP as a substrate for organophosphatases. Instead, DiFMUP is disclosed as a substrate for phosphatase or glucosidase activity. As noted above, one of skill in the art would have no reason to believe that substrates for phosphatases would also be substrates for organophosphatases. In fact, the present specification demonstrates that DiFMUP is not a suitable substrate for paraoxonase, an organophosphatase, due to “significant [paraoxonase] independent hydrolysis.” Spec. at ¶ [0095]. Thus, one of skill in the art would not consider DiFMUP a substrate for organophosphatases.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**C. U.S. Patent No. 4,659,657 to Harnisch *et al.***

Claims 57-93 stand rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. Patent No. 4,659,657 to Harnisch *et al.* According to the Examiner, Harnisch “discloses the use of 3-substituted umbelliferyl phosphates to detect organophosphatase. The 3-position substituent can be phenyl, heteroaryl, cyano etc.” Office Action at 3. Applicants respectfully traverse this ground of rejection.

Harnisch fails to teach or suggest the claimed invention for the same reasons that Gee fails to teach or suggest the claimed invention. Generally, Harnisch does not teach or suggest the same compounds as claimed, and there is no evidence or explanation as to why one of skill in the art would modify the Harnisch compounds to arrive at the claimed compounds. Moreover, Harnisch discloses substrates for phosphatase. Because organophosphatases and phosphatases are distinct classes of enzymes, one of skill in the art would have no reason to believe that Harnisch’s phosphatase substrates would also be substrates for organophosphatases.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

### CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration is requested, therefore. Also, Examiner Dentz is invited to contact the undersigned directly, should any issue warrant further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required regarding this application under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany the response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extensions of time are needed for timely acceptance of submitted papers, Applicants hereby petition for such extension under 37 CFR §1.136 and authorize payment of any such extensions fees from the deposit account.

Respectfully submitted,

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